## REMARKS

Claims 1-8 and 10-16 are pending and under consideration. With this Amendment, claim 8 is being amended. Thus, after entry of this Amendment, claims 1-8 and 10-16 are pending and under consideration. The amendment, as well as the rejections raised in the Office Action, are discussed in more detail, below.

Applicants note with appreciation that the nonstatutory obviousness-type double patenting rejection of claims 1-14 over claims 1-16, 19, 20 and 25-41 of U.S. Patent No. 6,193,951 to Ottoboni *et al.* has been withdrawn pursuant to page 2 of the Office Action.

Applicants note with appreciation that the nonstatutory obviousness-type double patenting provisional rejection of claims 1-14 over claims 3, 16-24 and 28-37 of U.S. patent application Serial No. 09/637,516 in view of EP 0 458 745 to Bichon *et al.* has been withdrawn pursuant to page 2 of the Office Action.

**The Amendments of the Claims**

The amendment of claim 8 corrects an obvious clerical error. No new matter is introduced by the amendment of claim 8. Accordingly, entry into the application is requested.

**Rejection Under 35 U.S.C. § 103(a)**

Claims 1-8 and 10-16 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over EP 0 458 745 to Bichon *et al.* ("Bichon") in view of U.S. Patent No. 4,466,442 to Hilmann *et al.* ("Hilmann") and further on view of WO 91/06287 to Berstein *et al.* ("Berstein"). Applicants traverse the rejection. For the sake of clarity, Applicants discuss briefly, to provide a background, each reference in a separate section below followed by remarks specifically directed toward the combination of references proposed in the Office Action.

**BICHON**

The Bichon reference is relied upon as teaching compositions comprising microballoons[1] filled with air or gas for use in ultrasound echography.[2] As correctly noted by the Office Action (page 5, lines 13-15), Bichon does not teach the use of nitrogen gas or microballoons having a membrane composed of two layers of polymers. In fact, Bichon teaches that, in some locations, his microballoons may have no layer of polymer at all! In particular, Bichon teaches that the "envelope" of his microballoon, *i.e.*, its shell, is "microporous": "the microporous structure of the microballoon envelope (pores of a few nm to a few hundreds of nm or more for microballoons envelopes of thickness ranging from 50-500 nm) ... The preferred range of pore sizes is about 50-2000 nm." (Col. 6, line 57 to col. 7, line 5). Bichon teaches that these pores are required so that, *inter alia*:

1. the porous microballoons "can readily accept pressure variations without breaking" (col. 7, lines 3-4);

2. microballoon cell-wall permeability can be controlled (col. 6, line 52), for example, such that an "increase [in] the size of the pores in the spheres [*i.e.*, microballoon] membrane through which the inside material will be evaporated" can be effected (col. 7, lines 23-25);

3. the "degree of porosity [of] the microballoons of this invention [can be adjusted so they] can be made stable in an aqueous carrier from several hours to several months and give reproducible echographic signals for a long period of time" (col. 7, lines 31-35); and

4. the micropores "provide more efficient echographic signal than corresponding non-porous vesicles" (col. 7, lines 44-46).

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[1] The Office Action refers to the microballoons of Bichon as "microparticles." Since the Bichon reference uses the term "microballoons" throughout, for example in the title, abstract and claims, that term is also used herein.

[2] Additional aspects of the Bichon reference noted by the Office Action are discussed further below.

The micropores in the polymer skin of the microballoons are achieved "by using the method disclosed in claims 17, 18 and subsequent claims" (col. 7, lines 6-8).

Turning now to Bichon's claims 17 and 18, the method for forming Bichon's microporous microballoons involves forming an oil-in-water emulsion, either with the polymer present in the hydrophobic (oil) phase (claim 18) or added in solution to the continuous water phase so that a layer of polymer forms around the oil phase (claim 17), and evaporating the solvent(s), including that encapsulated through the micropores.

**HILMANN**

From even the title of Hilmann, "Carrier Liquid Solutions for the Production of Gas Microbubbles ... ", it is clear that Hilmann teaches his microbubbles are not formed from any solid, such as a protein and/or a synthetic polymer. Rather, Hilmann's microbubbles are formed from a solution substantially free of undissolved solids that is made up of a mixture of (a) a solution of at least one tenside, *i.e.*, a surface-tension-imparter, and (b) a solution of a viscosity raising component. (*See, e.g.*, Abstract; col. 2, lines 42-56; col. 3, lines 8-35; claims 1 and 18). A gas is used to form the microbubbles from the solution mixture (col. 3, line 49 to col. 4, line 40). The sterile gas can include air, carbon dioxide, oxygen and/or nitrogen (col. 4, lines 41-44).

The Office Action contends "Hilmann *et al.* teach that nitrogen is a preferred gas for incorporation into microparticles for use in echography" (Office Action page 5, lines 16-17). Applicants disagree. Hilmann clearly teaches that while "sterile air" or a "physiologically acceptable sterile gas or mixture of gasses, *e.g.*, carbon dioxide, oxygen, nitrogen, noble gases, or mixtures thereof" can be used (col. 4, lines 41-44), "[s]terile air, carbon dioxide, and/or oxygen are preferred gases" (col. 4, lines 44-46, emphasis added). Thus, nitrogen is not taught among the preferred gases of Hilmann.

**BERSTEIN**

"[T]he [patent's] specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.' ... "[t]he best source for understanding a technical term is the specification from which it arose ... ." *Phillips v. AWH Corp.*, 75 USPQ2d 1321, 1327-1328 (Fed. Cir. 2005) (citations omitted). *See also, In re Fout*, 213 USPQ 532 (CCPA 1982) ("Claims must always be read in

light of the specification. Here, the specification makes plain what the appellants did and did not invent ... .").

The microspheres taught by Berstein are matrix particles that are solid. They do not have hollow cores. This is apparent from the explicit and unambiguous definition of microspheres provided at page 7, lines 7-8 of the reference: "Microspheres are solid spherical microparticles ... ."

Berstein further teaches: "Unless otherwise noted, the term microspheres can be used to encompass microcapsules ... ." (page 7, lines 11-13). Applicants can find no definition of "microcapsules" provided in Berstein. However, in his "Background of the Invention" section of the specification, Berstein refers to EP 0077956 of Tanabe Seiyaku Ltd. ("EP '956")[3] in the context of EP '956 describing "the use of zein and other proteins as enteric coatings for microcapsules, formed using standard techniques for coating, *i.e.*, spray coating or dipping" (page 2, lines 19-22, emphasis added). EP '956, a copy of which is included with the Supplemental Information Disclosure Statement accompany this response, teaches that its microcapsules are solid, in accord with the knowledge of one of ordinary skill in the art. In particular, EP '956 teaches that its enteric microcapsules are prepared by coating, in a dispersion, its core particles with ethyl cellulose from solution, adding the enteric material to the dispersion, and "further cooling the dispersion containing the enteric polymer material until the resultant embryonic microcapsules shrink and become solid by solvent loss from the coating walls ... " (page 2, line 25 to page 3, line 14, emphasis added; *see also* page 9, lines 23-26, emphasis added: "embryonic microcapsules are shrunk and become solid by solvent loss from the coating walls, thus giving stable ethyl cellulose microcapsules"; claim 1, emphasis added: "ethylcellulose microcapsules comprising (i) particles of a core material and (ii) ethylcellulose coating walls deposited on and around said particles of the core material").

Additionally, the emulsion method Berstein discloses clearly form microspheres that are solid. For example, in the procedure taught on page 10, lines 5-36, the "compound to be

[3] Berstein also refers to the microcapsules of EP 0158277 of Hoechst AG (page 2, lines 14-18); however, that reference is in the German language and Applicants are not aware of any English language counterpart.

incorporated" and a protein solution are introduced into a continuous phase, such as vegetable oil, which is immiscible with the solvent and does not dissolve the protein. The solvent is removed "under conditions forming microspheres" (page 10, lines 26-29, emphasis added). Surfactants are taught to be useful for adjusting the size of the protein microspheres that are being formed (page 10, lines 20-22).

Moreover, the Examples Berstein discloses clearly form microspheres that are solid. In particular, in Example 1 (page 20, line 20 to page 21, line 6), zein microspheres incorporating 4.8% or 9% solid zinc insulin (based on the weight of zein, page 20, lines 22-23) of mean particle diameter 3.2$\mu$m (page 20, line 32) are formed by adding a mixture of ethanol, the zein and the zinc insulin to a continuous corn oil phase. Berstein teaches that the "insulin was added as particles since insulin is insoluble in ethanol" (page 20, lines 30-31). Microspheres having diameters of between 1$\mu$m and 20$\mu$m were formed (page 21, lines 5-6).

Thus, it is clear that, in light of these various teachings within his specification, the microspheres (and/or microcapsules) disclosed by Berstein are solid; they do not have hollow cores.

In light of these teachings, Applicants respectfully submit that the Office Action's contention (on page 6, lines 18-19) that "Berstein *et al.* teach that the microparticles can be used in echography when a gas is incorporated into the microparticles" is an over-simplification of Berstein's teachings to the point of inaccuracy because the law requires that a reference must be evaluated as a whole, *i.e.*, disclosures in the reference that diverge from and teach away from the invention cannot be disregarded. "It is impermissible within the framework of [a] section 103 [rejection] to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 147 USPQ 391, 393 (CCPA 1965) (emphasis added). In *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, the Federal Circuit found error in the court below engaging in improper hindsight analysis based on selecting only an "isolated" disclosure of a reference because

> Barnes-Hind selected a single line out of the Caddell specification to support the above assertion. ... This statement, however, was improperly taken out of context. ... A full appreciation of Caddell's statement requires consideration of the immediately following sentences in the same paragraph and the paragraph after that. ... The district court improperly viewed an isolated line in Caddell in light of the teaching of the '814 patent to hold for obviousness. This is improper hindsight analysis.

230 USPQ 416, 419-420 (Fed. Cir. 1986).

The Office Action contends that "Berstein *et al.* teach that the microparticles can be used in echography when a gas is incorporated into the microparticles ..." (Office Action page 6, lines 18-19). Berstein does mention the incorporation of air specifically, not a gas generally: "Imaging agents including ... air, can also be incorporated. Air can be encapsulated by sonicating or agitating the protein solution before making the microspheres." (Page 6, lines 10-14). However, Berstein never reconciles this isolated mention of incorporating air with his repeated and consistent teaching of solid microspheres, including his definition of microspheres as solid spherical microparticles.[4] Applicants again emphasize the legal prohibition against focusing on a "single line" or "isolated line" of a reference as opposed to "consideration of the immediately following sentences in the same paragraph and the paragraph after that," *i.e.*, the entire teaching of the reference.

Therefore, the teachings of Berstein in which Berstein requires that, *inter alia*, his microspheres are solid - they do not have hollow cores - cannot legally be excluded or ignored when characterizing and fully appreciating what Berstein fairly suggests.

**COMPOSITION CLAIMS 1-8 AND 10-16**

**Remarks Concerning Multiple Layer Shells**

The Office Action contends that it would have been obvious to one of ordinary skill in the art at the time the instantly claimed invention was made "to produce a multilayer microparticle comprising the polymers of Bichon *et al.*, to fill the core of the microparticles with

[4] Although Berstein never reconciles this isolated mention of incorporating air with his repeated and consistent teaching of solid microspheres, Bichon teaches "solid microparticles (in the 0.1 to 1$\mu$m range) of the same sugars [*i.e.*, maltose, dextrose, lactose or galactose] containing entrapped air" (col. 2, lines 15-16; emphasis added).

nitrogen." Office Action page 6, lines 7-9. For the sake of argument, Applicants assume that the Office Action contends that the suggestion for "multilayers" arises from Berstein, as the Office Action admits "Bichon *et al.* do not teach a microparticle with a membrane comprised of two layers of the polymers" (Office Action page 6, lines 14-15) and contends that "Berstein *et al.* teach that the same polymers exemplified by Bichon *et al.* can be layered to form multilayer microparticles" (Office Action page 6, lines 20-22).

As discussed in detail above, Bichon teaches that the "envelope" of his microballoon is necessarily "microporous." Berstein teaches just the opposite! For example, Berstein's Example 15 teaches a "[c]omparison made by precipitation in water [*i.e.*, another method] with microspheres made by phase separation and solvent evaporation [*i.e.*, Berstein's method; *see* page 29, lines 30-31; page 7, lines 20-22]." Berstein teaches that the "spheres formed by water precipitation were much more porous and therefore of lower density" (page 29, lines 31-32). Thereafter, Berstein concludes that "the [precipitation in water] process [that forms much more porous microspheres] is not useful for efficient encapsulation of macromolecules nor do the resulting microspheres have the same appearance or characteristics as the microspheres formed by the phase separation, solvent evaporation techniques [of Berstein] described herein" (page 29, lines 33-37, emphasis added). Thus, Berstein teaches away from porous microspheres, the very microporous microspheres that Bichon discloses are required. Teaching away is "strong evidence of unobviousness." *In re Hedges*, 228 USPQ2d 685, 687 (Fed. Cir. 1986). A reference cannot suggest a limitation if it teaches away from the claimed invention. *In re Geisler*, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

Therefore, legally there can be no reason to combine the Bichon and Berstein references. Case law provides that if a reference teaches away from combining with another reference, then there is no suggestion to combine. For example, in *Tec Air, Inc., v. Denso Manufacturing Michigan Inc.*, the Federal Circuit held that "[t]here is no suggestion to combine, however, if a reference teaches away from its combination with another source" and that "[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant ... [or] if it suggests that the line of

development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." 52 USPQ2d 1294 (Fed. Cir. 1999).

Only for the sake of argument, even if Berstein's "multilayer" microsphere teaching were to be combined with Bichon's microporous envelope teaching as the Office Action suggests (*see, e.g.*, Office Action page 6, lines 10-12), the very act of adding another polymer layer over Bichon's microporous envelope would serve to seal the envelope's pores, thereby negating the microporosity of his microballoons that Bichon teaches is required. The Federal Circuit has held that if a proposed modification would render the prior art apparatus inoperable for its intended purpose, the prior art teaches away from the proposed modification. *See In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Additionally, MPEP § 2143.01 states: "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modifications." Therefore, as the Office Action's proposed combination would require modification of Bichon's microporous envelope - coating it with another layer thereby rendering it nonporous - and such modification would render Bichon's microballoons unsatisfactory for their intended purpose, Bichon teaches away from such modification and, *e.g.*, there can be no suggestion or motivation to make the proposed modification.

Furthermore and only for the sake of argument, even if Berstein's "multilayer" microsphere teaching were to be combined with Bichon's microporous envelope teaching as the Office Action suggests, because such modification would so radically alter the porosity of Bichon's microballoons, thereby rendering them unsatisfactory for their intended purpose, there could be no reasonable expectation of success to one of ordinary skill in the art were such modification to be effected.

In contrast to Bichon, instant independent claim 1 is directed to a composition comprising a plurality of microparticles. The microparticles comprise a shell enclosing a gas-filled hollow core. The shell comprises two layers: an outer layer composed of a cross-linked amphiphilic protein and an inner layer composed of a synthetic biodegradable polymer. In instant independent claim 12, the shell comprises two layers: an outer layer composed of glutaraldehyde cross-linked human serum albumin and an inner layer composed of polylactide.

**Remarks Concerning Hollow vs. Solid Microparticles**

The Office Action contends that "[o]ne of ordinary skill in the art would have been motivated to derive ... microparticles comprising a shell enclosing a gas filled hollow core, comprising an outer layer composes (*sic*) of cross-linked amphilic (*sic*) protein and an inner layer composed of biodegradable synthetic polymer because ... Bichon teach that ... the microparticles are filled with air or gas .... Bernstein (*sic*) teach that microspheres can be made as a polymer core within the protein microsphere ..." (Office Action page 9, lines 10-18).

As discussed above, Bichon teaches microballoons filled with air or gas. Berstein teaches just the opposite! As discussed in detail above, Berstein requires that, *inter alia*, his microspheres are solid - they do not have hollow cores – and this requirement cannot legally be excluded or ignored when characterizing and fully appreciating what Berstein fairly suggests. In fact, Berstein defines his microspheres as "solid spherical microparticles." Thus, Berstein teaches away from hollow microspheres, the very hollow microspheres that Bichon requires so that they can be gas-filled. Teaching away is "strong evidence of unobviousness." *In re Hedges*, 228 USPQ2d 685, 687 (Fed. Cir. 1986). A reference cannot suggest a limitation if it teaches away from the claimed invention. *In re Geisler*, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

Therefore, legally there can be no reason to combine the Bichon and Berstein references. As discussed above and which principles are equally applicable here, the Federal Circuit's case law, such as *Tec Air, Inc., v. Denso Manufacturing Michigan Inc.*, provides that if a reference teaches away from combining with another reference, then there is no suggestion to combine.

Only for the sake of argument, even if Berstein's "solid" microsphere teaching were to be combined with Bichon's "hollow microballoon" teaching as the Office Action suggests (*see, e.g.*, Office Action page 6, lines 10-12), the very act of making Bichon's microballoons solid would serve to negate their ability to serve as imaging agents for echography, the primary focus of his disclosure.

As discussed above, as the Federal Circuit has held in *In re Gordon*, if a proposed modification would render the prior art apparatus inoperable for its intended purpose, the prior

art teaches away from the proposed modification. As also discussed above, as the MPEP states in § 2143.01, if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modifications. Therefore, as the Office Action's proposed combination would require modification of Bichon's hollow microballoons - making them solid - and such modification would render Bichon's microballoons unsatisfactory for their intended purpose, Bichon teaches away from such modification and, *e.g.*, there can be no suggestion or motivation to make the proposed modification.

In contrast to Bichon, instant independent claim 1 is directed to a composition comprising a plurality of microparticles. The microparticles comprise a shell enclosing a gas-filled hollow core. The shell comprises two layers: an outer layer composed of a cross-linked amphiphilic protein and an inner layer composed of a synthetic biodegradable polymer. In instant independent claim 12, the shell comprises two layers: an outer layer composed of glutaraldehyde cross-linked human serum albumin and an inner layer composed of polylactide.

**Remarks Concerning Cross-linking**

The Office Action contends that "[o]ne of ordinary skill in the art would have been motivated to derive ... microparticles comprising a shell enclosing a gas filled hollow core, comprising an outer layer composes (*sic*) of cross-linked amphilic (*sic*) protein and an inner layer composed of biodegradable synthetic polymer because ... Bichon teach that cross-linking proteins, such as albumin, with glutaraldehyde is an art-recognized method of forming microparticle membrane shells ..." (Office Action page 9, lines 10-16).

In particular, the Office Action contends that "Bichon *et al.* teach that cross-linking proteins, such as albumin, with glutaraldehyde is an art-recognized method of forming microparticle membrane shells" (page 5, lines 4-6) and cites to column 3 of Bichon, which discloses: "The microspheres [after they are formed] are stabilized by denaturation of the membrane ... for instance by ... chemical means, *e.g.* by reaction with formaldehyde or glutaraldehyde" (col. 3, lines 25-29). However, in teaching away from this, Berstein teaches just the opposite!

For example, Berstein teaches, at page 1, lines 20-29 in connection with protein microspheres, that "[m]ost are crosslinked in solution using glutaraldehyde, or hardened at elevated temperatures. Unfortunately, there are problems with significant loss of biological activity of incorporated materials and lack of controlled size and *in vivo* degradation rates" (emphasis added). Furthermore, Berstein teaches "when modification of the protein using agents such as glutaraldehyde for crosslinking of the protein is desirable, the protein is treated prior to incorporation of the compound to be delivered and formation of the microspheres" (page 13, lines 17-20, emphasis added). Thus, Berstein teaches away from what Bichon discloses - the reaction of the protein of already-formed microspheres with glutaraldehyde. (*See also,* Berstein page 19, lines 17-18, emphasis added: "Proteins can be crosslinked prior to forming the microspheres."; page 4, lines 34-37, emphasis added: "The process for making the [Berstein] microspheres from a protein solution does not require high temperature heating or cross-linking which could degrade material to be incorporated.").

Therefore, legally there can be no reason to combine the Bichon and Berstein references. As already discussed above, case law provides that if a reference teaches away from combining with another reference, then there is no suggestion to combine.

In contrast, instant independent claim 1 is directed to a composition comprising a plurality of microparticles and a sugar. The microparticles comprise a shell enclosing a gas-filled hollow core. The shell comprises two layers: an outer layer composed of a cross-linked amphiphilic protein and an inner layer composed of a synthetic biodegradable polymer. Instant independent claim 12 is directed to a composition comprising a plurality of microparticles, glycine and polyethylene glycol 3350. The microparticles comprise shells enclosing a gas-filled hollow core. The shells comprise an outer layer composed of glutaraldehyde cross-linked human serum albumin and an inner layer composed of polylactide. In each instance, it is clear that because the instant microparticles are prepared starting from a solution of the outer biomaterial (*see, e.g.*, page 7, lines 10-14; page 8, lines 1-6; Examples 9 and 11 of the present specification), crosslinking cannot occur until after the microparticles are formed. This is contrary to what the Berstein reference in the proposed combination teaches.

Accordingly, for the reasons described above, it is submitted that the combination of references cited by the Office Action does not render instant independent claims 1 and 12 obvious. Dependent claims 2-8, 10, 11 and 13-16 are likewise non-obvious over the cited references for the same reasons. Withdrawal of the rejection is therefore requested.

**Non-Statutory Double Patenting Provisional Rejection**

Claims 1-8 and 10-16 stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of copending application Serial No. 10/977,100 ("the '100 application").

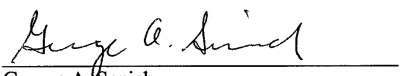
Applicants note that the '100 application was filed on October 28, 2004, which is after the date on which the instant application was filed - October 20, 2003. Pursuant to MPEP § 804(I)(B)(1), when a provisional double patenting rejection against a later-filed application is the only outstanding rejection in the earlier-filed application, and the later-filed application is still under rejection, the provisional double patenting rejection should be removed and the earlier-filed application permitted to issue. A review of PAIR indicates that, to date, no Office Action has been mailed in the '100 application. Accordingly, it is requested that the provisional double patenting rejection over the claims of the '100 application be held in abeyance until such time as claims in the instant application would be otherwise allowable, so that the Patent Office can then consider the application of MPEP § 804(I)(B)(1) to the instant application.

**Conclusion**

Claims 1-8 and 10-16 are believed to satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly requested.

No fees beyond those specified in the accompanying documents are believed to be due in connection with this Amendment. However, the Director is authorized to charge any additional fees that may required, or credit any overpayment, to Dechert LLP Deposit Account No. 50-2778 **(Order No. 375430-002T1D1C1 (355479))**.

Respectfully submitted,



Date: February 27, 2008

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